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Familial Aplasia/Hypoplasia of Pelvis, Femur, Fibula, and Ulna With Abnormal Digits in an Inbred Pakistani Muslim Family: A Possible New Autosomal Recessive Disorder With Overlapping Manifestations of the Syndromes of Fuhrmann, Al-Awadi, and Raas-Rothschild

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We describe four affected children belonging to a large, highly inbred Muslim family originating from the North West Frontier Province of Pakistan. All children have a similar pattern of skeletal abnormalities, including aplasia/hypoplasia of the ulnae, hypoplasia of the pelvis, aplasia/hypoplasia of the femora, fibular aplasia, and variable digital abnormalities and absent/dysplastic nails. The phenotype overlaps with the syndromes of Fuhrmann, Al-Awadi, and Raas-Rothschild. The present and previously reported families probably share the same geographic and racial origin, indicating a common genetic basis of the reported skeletal abnormalities in these limb-pelvis aplasia and hypoplasia syndromes. A possibility of a new autosomal recessive syndrome in the present family cannot be excluded. Further delineation and molecular studies are required to clarify the genetic cause and phenotypic variation in Fuhrmann, Al-Awadi, and Raas-Rothschild syndromes. Am. J. Med. Genet. 70:107–113, 1997.

KEY WORDS: autosomal recessive; consanguinity; FFU complex; Fuhrmann syndrome; Al-Awadi syndrome; Raas-Rothschild syndrome; proximal focal femoral deficiency (PFFD)

INTRODUCTION

Congenital developmental defects of femur, fibula, ulna, fibular rays, and ulnar rays (FFU complex) are uncommon, and are probably causally heterogeneous. The term proximal focal femoral deficiency (PFFD), coined by Aitken [1969], can be part of the FFU complex [Lenz and Feldmann, 1977]. Autosomal recessive inheritance was suggested in the FFU complex [Zlotogora et al., 1983], although most cases are sporadic [Kühne et al., 1967; Lenz and Feldmann, 1977]. A subsequent case report [Fuhrmann et al., 1980] described an association of poly-, syn-, and oligodactyly with aplasia and hypoplasia of femur and fibula, but without developmental abnormalities of the ulna and ulnar rays. Familial occurrence of similar combinations of developmental skeletal abnormalities was described with thoracic "dystrophy" (the Al-Awadi syndrome) [Al-Awadi et al., 1985], and pelvis hypoplasia (the Raas-Rothschild syndrome) [Raas-Rothschild et al., 1988].

We report on a large, consanguineous Muslim family, originating from the North West Frontier Province of Pakistan, in which four children were born with malformations of the forearms, hands, fingers, pelvis, and lower limbs. All shared a variable degree of aplasia/hypoplasia of the femur, fibula, and ulna associated with digital abnormalities, including brachydactyly of the fourth and fifth fingers and toes bilaterally with hypoplasia of fingernails. Complex and multiple consanguinity in this family strongly supports autosomal recessive inheritance. The clinical findings in this family are discussed in the context of previous reports.

CLINICAL REPORTS

The family (Fig. 1) came to our attention following the birth of the proposita, V-7. Two other related children (V-3 and V-5) were then ascertained, born with similar developmental defects of the limbs. II-2 and

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II-8 were sibs, and therefore their parents could be the common ancestors to this family. Inbreeding coefficients among the various intermarriages are similar to the "first cousins," "second cousins," or "first cousins once removed" relationships (Table I).

The proposita (V-7), was born with good Apgar scores by emergency cesarean section at 36 weeks, following an uneventful pregnancy. Bilateral upper and lower limb malformations were noted, along with anomalies of the head and face (Fig. 2a). The head circumference was just above the 3rd centile, with normal sutures and an open anterior fontanelle; also noted were hypertelorism, wide-set eyes, depressed nasal bridge, a hypoplastic midface, mild micrognathia, and short neck. External genitalia were normal.

Upper limb abnormalities in V-7 (Fig. 2b) included bowing of the forearms, short fingers on both hands, and post-axial polydactyly on the left hand. Limitation of extension, supination, and pronation was present. Both hands were small, with hypoplastic fingernails.

There was a pilonidal dimple over the lower spine. Both thighs were bowed (Fig. 2c). Moreover, a traumatic fracture of the left femur resulted in an acutely bent left upper femur. Both legs were bowed. Bilateral talipes with equinovarus was present with lack of fourth and fifth toes, and short and stubby first, second and third toes with hypoplastic toe nails (Fig. 2d).

A roentgenographic skeletal survey (Fig. 3a, b) confirmed hypoplasia of femora, fibulae, and ulnae and hypoplasia of the ulnar and fibular rays, including the fourth and fifth digits in hands and feet. Ultrasound examination of the abdomen soon after birth did not show any abnormality. Other investigations included a normal chromosome complement (46,XX), specifically excluding premature centromere expansion. Follow-up review at age 8 months and 3 years indicated normal neurological development with physical growth along the 3rd centile.

TABLE I. Inbreeding Coefficients in the Pakistani Muslim Family*

Parents	R	Offspring	F
IV-3:IV-4	1/32	V-1 to V-4	1/64
III-5:IV-7	1/16	V-5, V-6	1/32
III-6:IV-8	1/16	V-7, V-8	1/32
IV-11:IV-15	1/8	—	1/16
IV-12:IV-13	1/8	V-9	1/16

*R = Coefficient of relationship; F = Coefficient of inbreeding.

Another affected child (V-3) was born to consanguineous parents (IV-3 and IV-4), belonging to another sibship. She was born with hypoplastic femora, fibulae, and ulnae, and syndactyly of the fourth and fifth digits of hands and feet (Fig. 4a). Roentgenographic examination confirmed hypoplastic pelvic wings, angulated short femora, and absent fibulae and ulnae (Fig. 4b).

She was treated for bilateral recurrent multiple renal calculi associated with low serum urate, increased hypoxanthine and xanthine levels with xanthinuria,

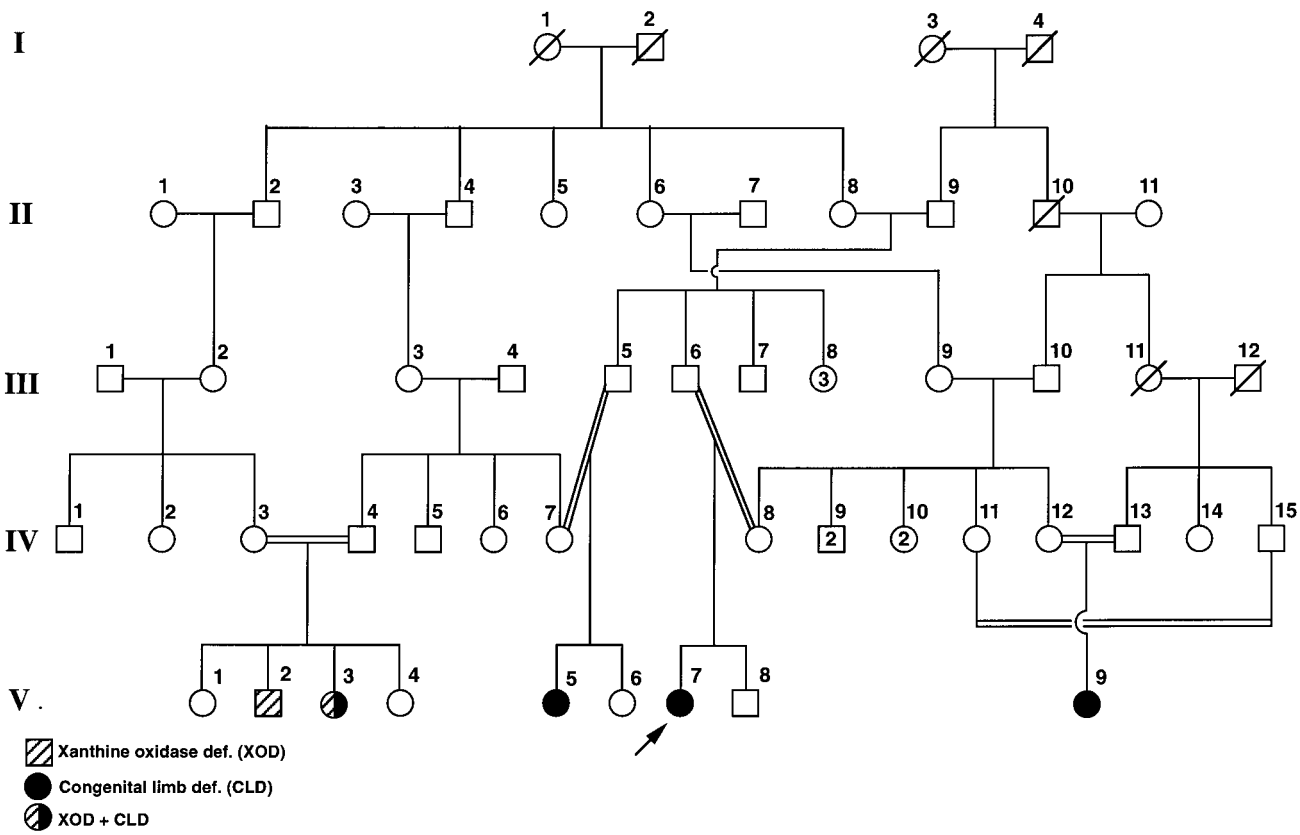

Fig. 1. Pedigree of the Pakistani Muslim family.

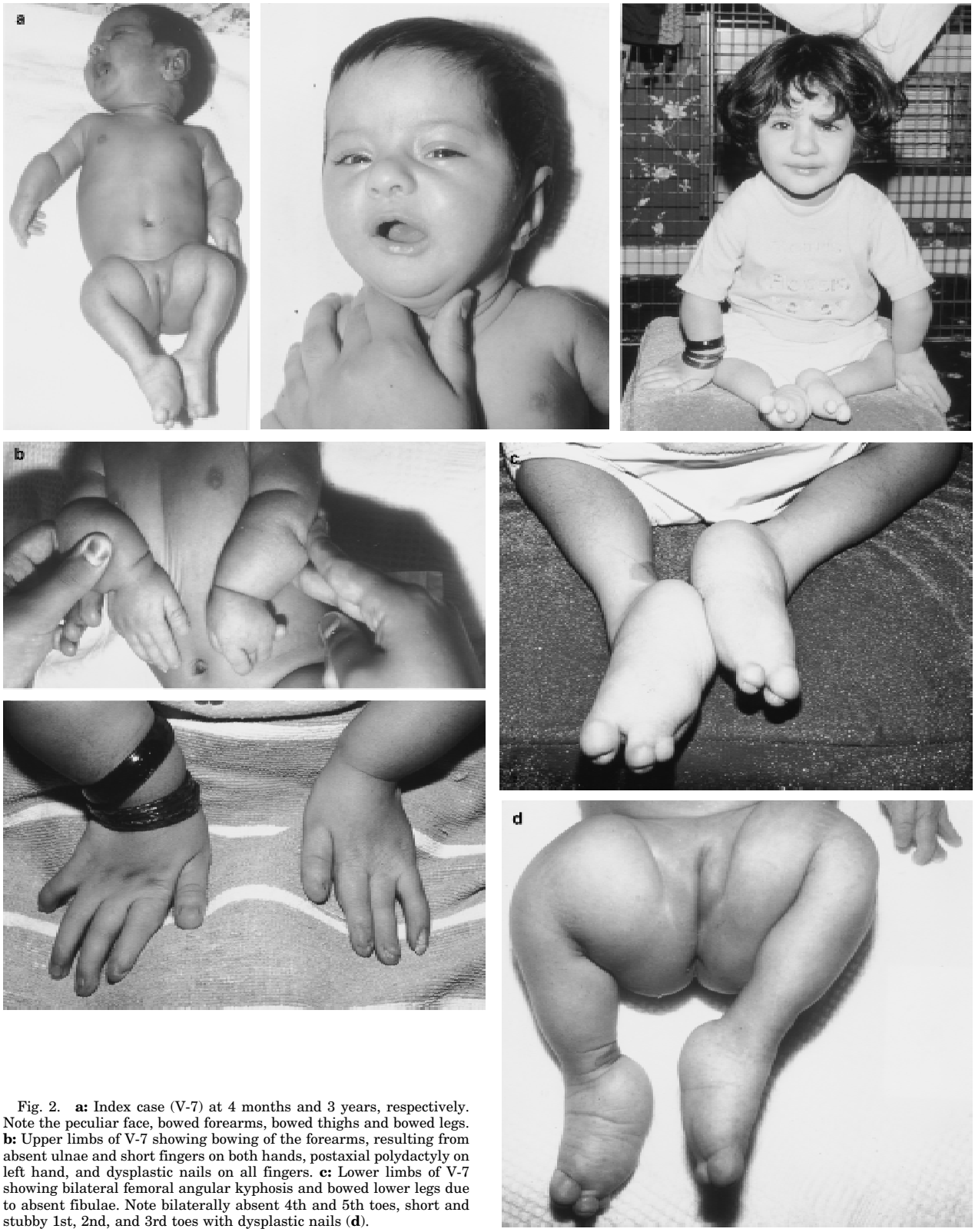

Fig. 2. **a:** Index case (V-7) at 4 months and 3 years, respectively. Note the peculiar face, bowed forearms, bowed thighs and bowed legs. **b:** Upper limbs of V-7 showing bowing of the forearms, resulting from absent ulnae and short fingers on both hands, postaxial polydactyly on left hand, and dysplastic nails on all fingers. **c:** Lower limbs of V-7 showing bilateral femoral angular kyphosis and bowed lower legs due to absent fibulae. Note bilaterally absent 4th and 5th toes, short and stubby 1st, 2nd, and 3rd toes with dysplastic nails (**d**).

due to underlying xanthine oxidase deficiency, also present in her older brother (V-2). She has had various forms of urological treatment for nephrolithiasis. An abdominal ultrasound examination soon after birth did not show any abnormality. Her brother (V-2) also has multiple recurrent nephrolithiasis, but does not have any congenital skeletal abnormalities.

The other affected child (V-5), was also born with

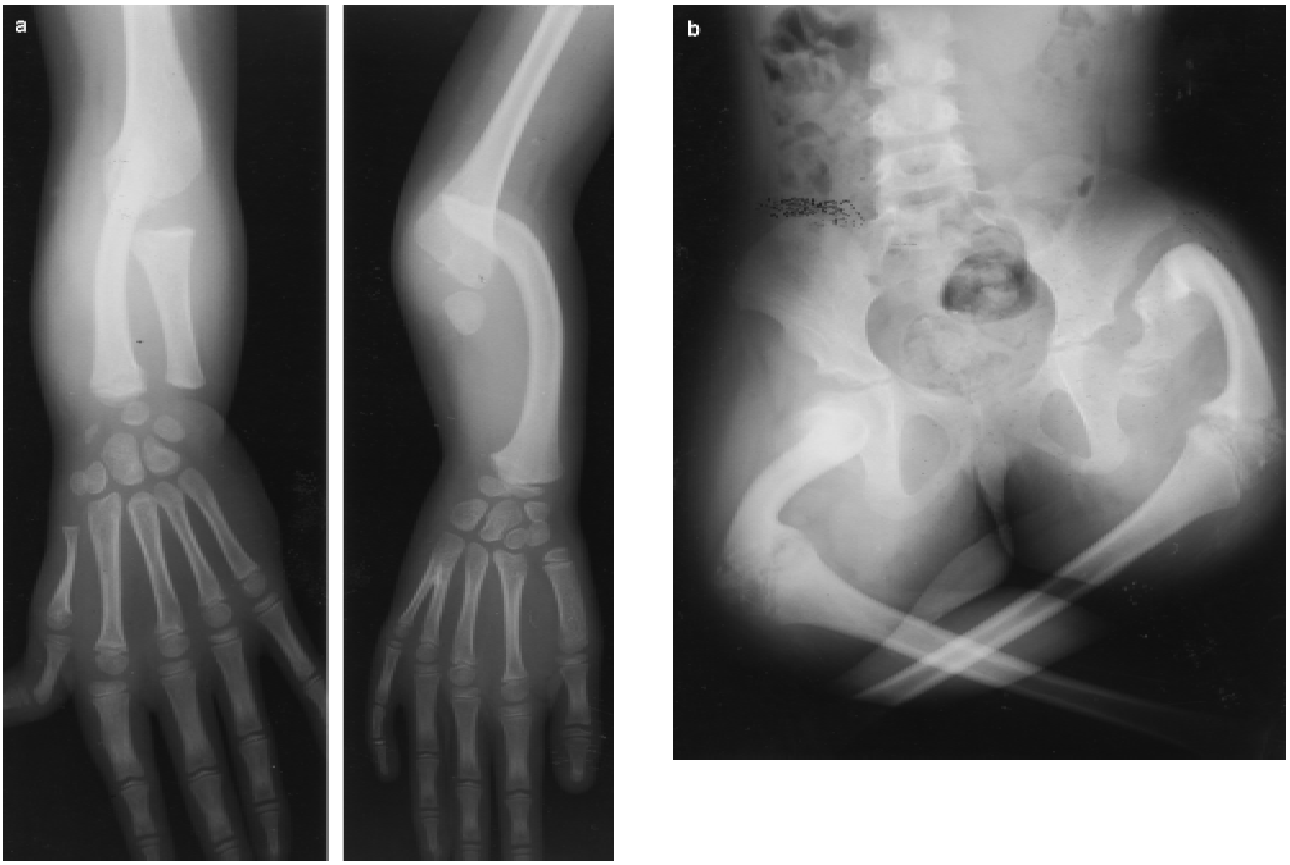

Fig. 3. **a:** Roentgenographs of V-3 showing short/absent ulnae, bowed radii, hypoplastic 4th and 5th metacarpals and correspondingly small phalanges. **b:** Lower limbs of V-3 showing bilaterally hypoplastic angulated femora and absent fibulae.

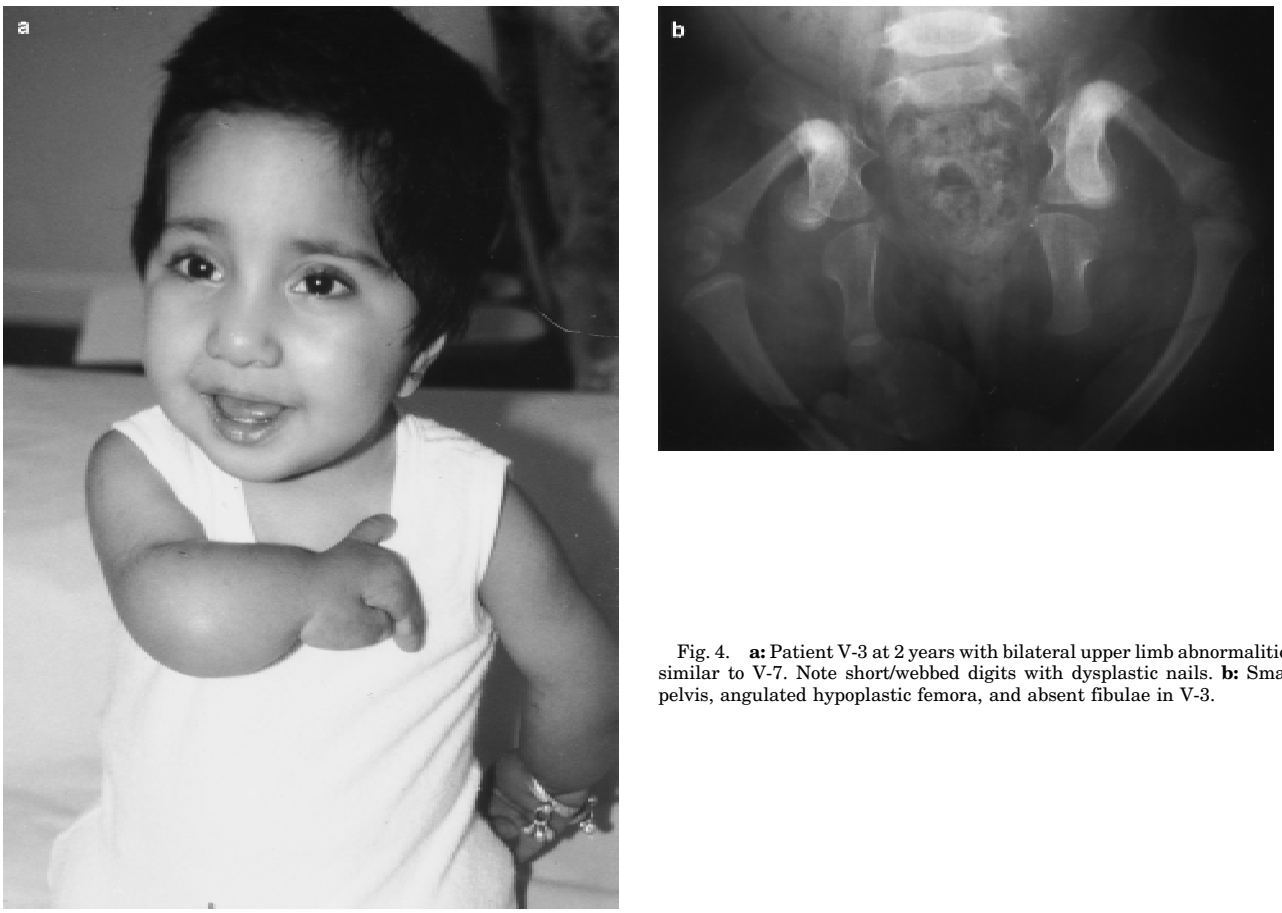

Fig. 4. **a:** Patient V-3 at 2 years with bilateral upper limb abnormalities similar to V-7. Note short/webbed digits with dysplastic nails. **b:** Small pelvis, angulated hypoplastic femora, and absent fibulae in V-3.

Fig. 5. Patient V-5 at 5 years showing **a:** lateral view which shows bilaterally abnormal short upper limbs, angulated hypoplastic femora, and bowed forearms and lower legs; **b:** ulnar deviation of both hands, with short stubby thumbs, distal hypoplasia of all fingers with dysplastic nails; **c:** closer view of right foot: note only one malformed toe with marked generalized hypoplasia of foot; left foot is also small (see a), with three round rudiments of fused and malformed toes.

absent/hypoplastic femora, fibulae, and ulnae (Fig. 5a). She closely resembles the index case, V-7, in having distal shortness of the upper limbs with ulnar deviation and hypoplasia of all fingers and dysplastic nails (Fig. 5b). Both lower limbs are deformed with extremely short femora and thin legs with short and misshapen feet, and short, stubby toes (Fig. 5c).

On examination of this child at 5 years of age, weight (15 kg) and height (64 cm) were below the 3rd centile, with a normal head size (50 cm). She has short and curved forearms, with the right thumb held in fixed extension and the left thumb in fixed flexion. She has no fingernails on the thumb and the first two fingers on both hands. In the lower limbs, she has extremely short femora and very thin and short legs with fixed flexion at both knees. The right foot is flexed in front of the pelvis and she tends to hold the left foot flexed behind the pelvis. She has only one toe on the right foot, and 3 misplaced digits on the left foot. The spine, pelvic and shoulder girdles, head, and neck are all normal. Radiologically she has similar bony abnormalities as in V-3. An abdominal ultrasound examination at age 4 years did not show any abnormality.

The fourth child (V-9) was born to another set of consanguineous parents (IV-12 and IV-13). The mother (IV-12) is the full sister of the mother of the proposita (IV-8). Her husband (IV-13) is a first cousin, the son of her paternal aunt. The pregnancy was interrupted at

26 weeks of gestation by spontaneous onset of labor. The female infant lived for 11 hours and had similar abnormalities of the forearms, hands, fingers, pelvis, and lower limbs as those referred to in the other affected members of the family. Further details are not available.

DISCUSSION

Developmental anomalies involving the pelvis, femoral shaft, fibula, and ulna commonly occur together [Warkany, 1970]. Most of these cases are sporadic. However, a syndromal combination of congenital limb deficiencies (CLDs) including congenital aplasia or hypoplasia of femur, fibula, and ulna [FFU] is described and is probably causally heterogeneous [Temtamy and McKusick, 1971]. The first large study was reported by Kühne et al. [1967] and included 55 previously reported and six new cases. The developmental defects included aplasia or hypoplasia of femur, fibula, ulna, ulnar, and fibular rays of variable degrees of severity and of irregular distribution. Limb abnormalities range from unilateral hemimelia to the involvement of either the upper or lower limbs.

PFFD represents a similar malformation, with deficiency of the proximal part of the femur as the chief defect. The survey of Westin and Gunderson [1969] documented absence of the fibula in more than half of the cases, approximately one quarter with upper limb abnormalities and the remaining one-fourth with variable limb defects. It has been reasonably argued that PFFD and FFU are the same condition [Lenz and Feldman, 1977], probably related to the fibular developmental field [Lewin and Opitz, 1986; Sorge et al., 1995]. A genetic basis of FFU syndrome was first suggested by Zlotogora et al. [1983], who described two sibs affected with the FFU complex, raising the possibility of autosomal recessive inheritance.

In 1980 and 1982 Fuhrmann et al. described four sibs with absent fibulae, right angle bowing of femora, absence of nails, and polydactyly in Turkish Christians of Arabic extraction. Although consanguinity was not recorded, the authors postulated autosomal recessive inheritance on the basis of the highly inbred ethnic origin of the family. Two possible further cases have been identified as similar to the original description of the Fuhrmann syndrome [Lipson et al., 1991]. The parents of one patient were Polish, but non-consanguineous, and the second patient was born to South Vietnamese refugees from an isolate of Baptists in a village in the Mekong Delta of South Vietnam. Parental consanguinity was inferred, but not confirmed. The Fuhrmann syndrome appears to be a distinct combination of developmental limb abnormalities, differing from FFU complex in lacking a consistent association of the ulna or ulnar rays.

Al-Awadi et al. [1985] and Raas-Rothschild et al. [1988] described a condition of severe limb deficiency, aplasia/hypoplasia of the pelvis, thoracic "dystrophy," and variable digit abnormalities. Similar patients have also had acrania [Schinzel, 1990; Chitayat et al., 1993], renal agenesis, meningocele, hypoplasia of the cerebellum [Camera et al., 1993] and abnormal development of the Müllerian system [Farag et al., 1993]. Phenotypic similarity, ethnic origin, and autosomal recessive inheritance suggest the existence of one or several similar entities the FFU complex, and the Fuhrmann, Al-Awadi, Raas-Rothschild, and Schinzel phocomelia syndromes.

The condition present in our patients is in many respects similar to FFU dysostosis, and the Fuhrmann and Al-Awadi/Raas-Rothschild syndromes. FFU dysostosis is an overwhelmingly sporadic disorder, and therefore probably a causally distinct entity. However, in view of autosomal recessive inheritance, possibly similar ethnic ancestry and phenotypic similarity to the Al-Awadi/Raas-Rothschild and Fuhrmann syndromes, the condition present in our patients may be the same entity; however, we can not rule out the existence of a previously undescribed entity.

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